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Review

# Ceftaroline: a comprehensive update

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ABSTRACT

Ceftaroline is a novel broad-spectrum cephalosporin antibiotic currently under US Food and Drug Administration (FDA) review for a new drug application (NDA), filed by Cerexa, Inc. (a wholly owned subsidiary of Forest Laboratories), for the treatment of complicated skin and skin-structure infections (cSSSIs) and community-associated pneumonia (CAP). The antibiotic acts by binding to penicillin-binding proteins in bacteria, consistent with other β-lactams. The antimicrobial spectrum of ceftaroline ranges from aerobic and anaerobic Gram-positive bacteria, including drug-resistant isolates of staphylococci, i.e. heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA), vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA), to anaerobic Gram-negative pathogens such as *Moraxella catarrhalis* and *Haemophilus influenzae* (including β-lactamase-positive strains), as well as bacteria with multiple resistance phenotypes. Ceftaroline fosamil is the prodrug that is rapidly dephosphorylated by in vivo plasma phosphatases to the active drug ceftaroline, which follows a two-compartmental pharmacokinetic model and is eliminated primarily by renal excretion, with a plasma half-life of ca. 2.5 h. Ceftaroline is well tolerated, which is consistent with its good safety profile similar to other cephalosporins in clinical trials. Thus, it would be a promising drug to fight multidrug-resistant superbugs such as *S. aureus* and *Streptococcus pneumoniae* for the treatment of cSSSIs and CAP.



## 1. Introduction

Ceftaroline fosamil [1–3] (synonyms PPI-0903 and TAK-599) is a novel, parenteral, broad-spectrum, bactericidal, advanced-generation cephalosporin that shows potent activity against many bacteria owing to its high binding affinity to penicillin-binding proteins (PBPs), especially PBP2a in meticillin-resistant *Staphylococcus aureus* (MRSA) and PBP2x in penicillin-resistant *Streptococcus pneumoniae* (PRSP) [4,5]. It has profound activity against the Gram-positive bacteria *S. aureus*, penicillin-intermediate *S. pneumoniae* (PISP) and PRSP, against respiratory Gram-negative pathogens such as *Moraxella catarrhalis* and *Haemophilus influenzae* (including β-lactamase-positive strains), as well as against bacteria with multiple resistance phenotypes [6–9]. Phase III clinical trials of ceftaroline were concluded in 2009 and data emerging from these studies were submitted by Cerexa, Inc. to the US Food and Drug Administration (FDA) for approval of new drug application (NDA) 200327 on 30 December 2009. Results demonstrated that it was well tolerated in patients and has a consistent safety profile reflective of other cephalosporins [10].

## 2. Historical background

In 2003, Ishikawa et al. discovered ceftaroline fosamil, which was developed by Takeda Chemical Industries Ltd. (Osaka, Japan), and an investigational new drug application was submitted in December 2004. More recently, on 8 September 2010, Forest Laboratories received FDA advisory committee approval for the treatment of complicated skin and skin-structure infections (cSSSIs) and community-associated pneumonia (CAP) following completion of phase III clinical trials. The developmental pathway of ceftaroline from cefozopran [11–14], a fourth-generation cephalosporin, as depicted in Fig. 1, resulted in the development of T-91825, which had potent anti-MRSA activity along with poor water solubility. This poor water solubility was due to the zwitterionic structural effect and was later rectified by applying the *N*-phosphonoamino prodrug strategy, which has good physiochemical properties in solid state and in solution [15].

## 3. Physiochemical properties

According to *International Nonproprietary Names for Pharmaceutical Substances (INN)*, ceftaroline fosamil is an anhydrous, acetate-free compound with the molecular formula $C_{22}H_{21}N_8O_8PS_4$ and a molecular weight of 684.68 atomic mass units (amu) [16]. The melting point of the prodrug as reported in the literature [4] is 221–223 °C (decomposed). Solubility of the prodrug in water is

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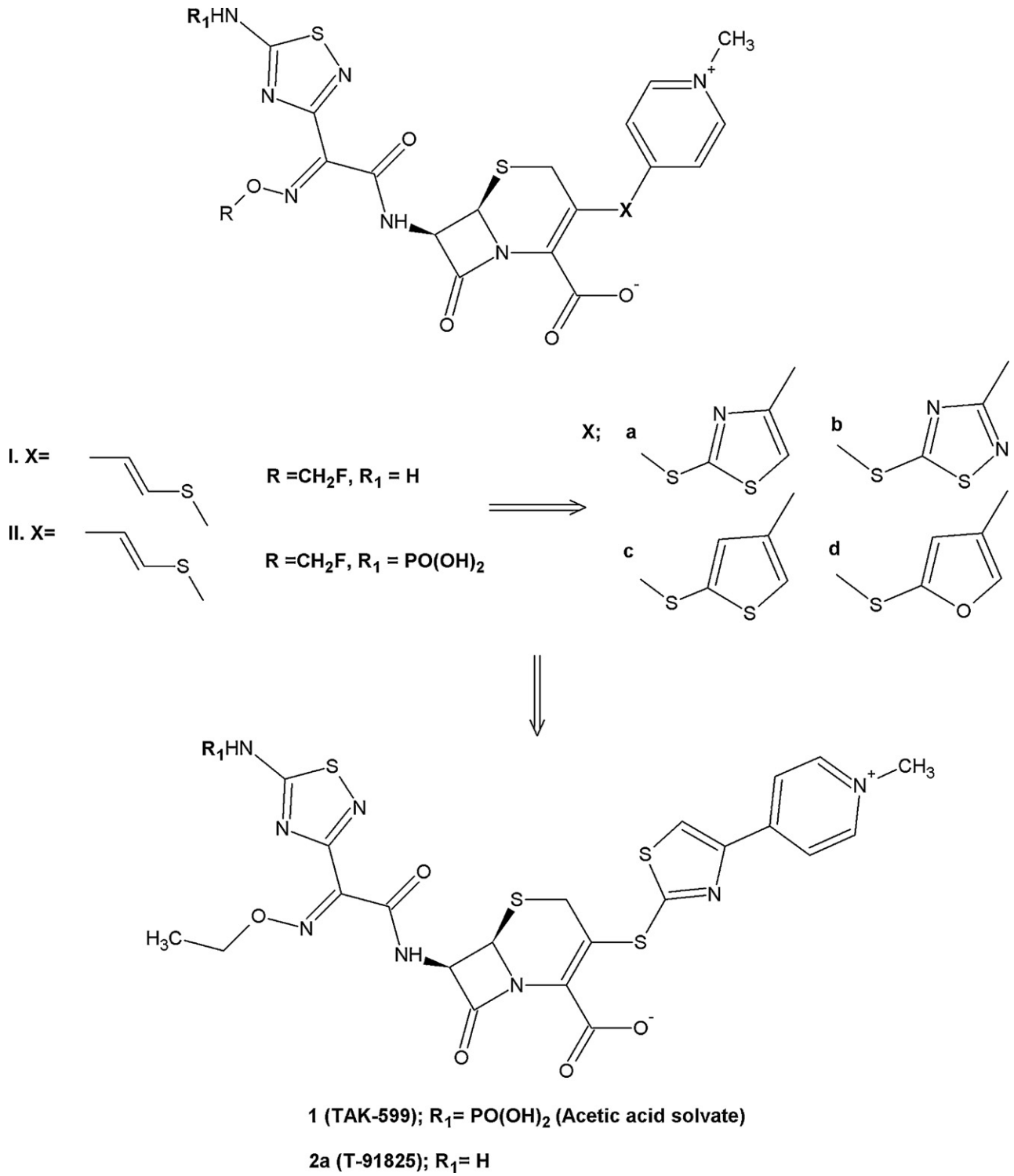


**Fig. 1.** Development route of ceftaroline, as spacer group X was changed from an aliphatic chain to a thio five-membered heteroaromatic (a–d).

better (>100 mg/mL) than that of ceftaroline (2.3 mg/mL) at pH 7.0, whilst maintaining good stability for a period of 8 h (purity >98%) at the same pH. In solid state it remains stable for a period of 4 months at 40 °C (purity >96%) [17].

## 4. Chemistry and structure–activity relationship

Ceftaroline is a β-lactam antibiotic that is chemically 3-[4-(1-methyl-4-pyridinio)1,3-thiazol-2-yl]thio-7β-[2-(5-phosphono -amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-ethoxyiminoacetamido]-3-cephem-4-carboxylate acetic acid solvate.

As observed with a variety of cephalosporins, variation in position 7 of the acyl amino side chain and substitution on the cephem ring contribute different activity profiles [18].

- The side chain containing an alkoxyimino group at the C-7 acyl moiety provided in vitro anti-MRSA activity, as it maintained affinity for PBP2a.